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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/770,943	01/25/2001	Eyal Raz	UCSD-173CON	8209

24353 7590 05/28/2008

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EXAMINER	
DUFFY, PATRICIA ANN	
ART UNIT	**PAPER NUMBER**
1645	

MAIL DATE	DELIVERY MODE
05/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/770,943	RAZ ET AL.	
	Examiner	Art Unit	
	Patricia A. Duffy	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-36 and 38-44* is/are pending in the application.

4a) Of the above claim(s) *40 and 42-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-36, 38, 39 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9-19-07 has been entered.

The amendment filed 9-19-07 has been entered into the record. However, it is noted that the amendment is not in compliance with 37 CFR 1.121 as claim 32 does not properly amend previous claim 32. Claim 32 as presented in the amendment of 9-19-07 has improperly deleted "[Y]" and "[Z]" from the base formula. Correction is required.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

Election/Restrictions

This record indicates that Applicants elected composition is the specie AAGGTT (response of 12-8-03) and autoantigen (response of 12-4-06). It is noted that only claims 32-36 and 38-39 currently read on the elected invention.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 40 and 42-44 are withdrawn from consideration as being directed to a non-elected invention as not comprising the elected species AAGGTT and autoantigen. See 37 CFR 1.142(b) and MPEP § 821.03.

Accordingly, claims 32-36, 38-39 and 41 are under examination.

Rejections Withdrawn

Claims 40, 42 and 43 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by Scholar et al (U.S. Patent No. 5,552,390 filed December 9, 1993) is withdrawn in view of the amendment to the claims.

Claims 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scholar et al (U.S. Patent No. 5,552,390 filed December 9, 1993) in view of Barsoum et al (WO 94/04686, published March 3, 1994) is withdrawn in view of the amendment to the claims.

Rejections Maintained

The rejection of claim 36 under 35 U.S.C. 103(a) as being unpatentable over Bennett et al (WO 91/16901, published November 14, 1991) in view of Barsoum et al (WO 94/04686, published March 3, 1994) is maintained for reasons made of record.

Applicants' arguments have been considered but are still not persuasive. Applicants argue that there is no explicit motivation to conjugate the peptide since the prior art did not perceive any difficulty in delivery of the antisense nucleic acid per se. This is again not persuasive, the use of cargo peptides to facilitate delivery was a well established technique in administering antisense therapy because it would facilitate and enhance delivery *in vitro* and *in vivo* as taught by the prior art. Further, *In re* Fine, 837 F.2d 1071, 1075, 5U.S.P.Q.2d 1959 (Fed. Cir. 1988) states that under section 103 a *prima facie* case of obviousness can be established by showing some objective teaching in the prior art **or *that knowledge generally available to one of ordinary skill in the art can lead the individual to combine the references***. See also *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Furthermore, the courts have held "The test of obviousness is not express suggestion of the claimed invention in any or all of the references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them." See *In re Rosselet*, 146 USPQ

183, 186 (CCPA 1965). "There is no requirement (under 35 USC 103(a)) that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *Motorola, Inc. v. Interdigital Tech. Corp.,* 43 USPQ2d 1481, 1489 (Fed. Cir. 1997). Finally, an obviousness determination is not the result of a rigid formula disassociated from the consideration of the facts of a case. Indeed, the common sense of those skilled in the art demonstrates why some combinations would have been obvious where others would not. See *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. , 2007 U.S. LEXIS 4745, 2007 WL 1237837, at *12 (2007) ("The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results."). In this case the predictable result is facilitating or enhancing movement of the antisense oligonucleotide into the cell. This composition is merely a combination of known elements, yielding predictable results.

The rejection is maintained.

Claims 32-35, 38, 39 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained for reasons made of record for claims 32-35, 38, 39 and 44.

Applicants arguments have been carefully considered but are not persuasive. Applicants reiterate the teachings of the specification that have already been considered. Applicants continue to argue switch to a Th2 response. This is again not persuasive, first because a switch in the immune response still provides an immune response against the autoantigen. This immune response will be as destructive as the immune response that initiated the autoimmune disease. Applicants argue that an ISS when administered alone or in an admixture with antigen as Exhibit 1 is evidence that an

IIS would not be effective in inducing a TH2 response. This is not persuasive, the IIS of the invention is inhibitory of activation of an immune response. A switch to a Th2 response still activates that immune system. The antibodies of the Th2 response will still be destructive. Applicant relies upon an Example 3 of the specification. This is not persuasive, it is not directed to the claimed invention. Further, it does not establish effective therapeutic intervention in an autoimmune disease. The example does not establish inhibition of the immune response. The immune response is still alive and well, antibody, albiet a different isotype is generated. Applicants essentially argue that a switch will be the cure-all for autoimmune disease. This is not persuasive because the art does not recognize that generation of a Th2 type immune response is effective to treat autoimmune disease. A review of the art shows that little is known about the induction of a Th2 response for the treatment of autoimmune disease. A review of the specification discloses that the method of the instant claims presumably treats Th1 autoimmune disease by administering an autoantigen or autoantibody conjugated to an ISS-ODN to skew the immune response towards Th2, from the Th1. This method is, again presumably, based on the theory that there exists a Thl/Th2 balance wherein increasing the Th1 or Th2 response decreases the other. First note that many investigators consider the Thl/Th2 paradigm an overly simplistic way to view highly complex systems. See for example Louzoun et al. (Journal of Autoimmunity, 17:311-321, 2001) and that therapeutic manipulation of the Th1-Th2 balance is inherently dangerous and unpredictable (Brunet et al and Wohlleban et al (Trends in Immunology 23(3):127-128, 2002). The art teaches that autoimmune Th1 responses can develop and continue even in the presence and high frequencies of Th2 cells (Hofstetter et al, Journal of Immunology 169:117-125, 2002). Therefore, it is clear that immune deviation does not predict a therapeutic effect and the Th2 autoantibodies can be pathogenic and exacerbate existing disease. Further, the generation of an autoimmune Th1 response in the presence of an existing Th2 repertoire indicates that the in vivo situation is highly complicated and not as simple as either a Th1 -

autoimmune disease versus Th2 – no autoimmune disease. Tisch et al (Proc. Natl. Acad. Sci., 91:437-738, 1994) teach that typically and autoimmune disease is diagnosed at a time when significant tissue damage has already occurred. At this point, the need is for a form of therapy that can prevent further damage and eliminate or block all or nearly all autoreactive T-cells It is possible however, that administering an antigen/peptide after pathogenic T cells have been activated may exacerbate the disease condition. Genain et al (Science, 274:2054-2056, 20 December 1996) teach that immune deviation and shift of a cytokine production from a Th1 pattern to a Th2 pattern increased titers of autoantibodies, increase pathogenic autoantibodies and exacerbate autoimmune disease (see abstract). As such, switch to the Th2 type cytokine response is not necessarily correlated with autoimmune disease therapy.

Applicants argue that the Office has not provided sufficient scientific reasoning. This is clearly not persuasive as the Office provided a plethora of scientific documents, documenting the unpredictability in attempting to modulate the immune response for the treatment of autoimmune diseases. Applicants also argue that is an IIS conjugate as claimed be capable of inducing a Th2-type of immune response in an individual. This is simply not commensurate with the specification. The claims are drawn to pharmaceutical compositions, and no pharmaceutical use for treatment or prevention of autoimmune disease using any conjugate as claimed has been enabled for reasons made of record. Applicants argue that Cho as drawn to an ISS (immunostimulatory) as opposed to the instant IIS (immunoinhibitory) enables this invention. This is again not persuasive, the claims are drawn to an immunoinhibitory conjugate of an autoantigens and the use of autoantigens alone or as conjugates is not predicable and the correlation of Th2 response with therapeutic effect in autoimmune disease is not set forth in the specification. Applicants invite the Office to provide affidaviats regarding stimulation of a primed Th1 response with autoantigen. Applicants are directed to Tisch et al above and Hoffstetter et al of record. Applicants dismiss all the references establishing the difficulty and

failures in the art in modulation of immune responses as a means for treatment of autoimmune disease (i.e. as it relates to the instant pharmaceutical composition) as not directly addressing the instant construct. It is noted however, the Office has appropriately cited evidence which is reason to doubt the objective truth of the statements contained in Applicants' specification. (*In re Marzocchi and Horton*, 169 USPQ 367 (CCPA 1971)). Applicants argue that the claims doe not recite autoantigens. This is not persuasive, the claims are drawn to a pharmaceutical composition comprising an autoantigen conjugate. The specification specifically discusses therapy of autoimmune diseases and particular autoimmune disease contemplated and clearly states such pharmaceutical compositions are useful for treatment of such autoimmune diseases. As such all the cited art highly relevant and directly on point to the claimed pharmaceutical compositions. Applicants argue that the since the generation of a Th1-type immune response using and ISS-allergen conjugate is efficacious the use of the IIS-autoantigen conjugate would also be efficacious. This is not persuasive, because Applicants are arguing apples and oranges. The antigens are not the same, the response is not the same and the nucleic acid is not the same.

Applicants argue post filing date references of Ho et al. These references are not persuasive because they are not drawn to the claimed invention claimed invention (IIS conjugated to autoantigen). The claimed invention must be enabled at the time and Ho et al do not address the claimed invention. The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

The specification fails to teach even one conjugate that is successful in generating modulated or switched cytokine response in an antigen-driven *in vitro* model relevant and correlative/predictive of treatment of autoimmune disease *in vivo*. The ability to switch the ability of an IIS-ODN to modulate the cytokine profile of naïve cells stimulated with

ISS-ODN *in vitro* is not reflective of the antigen driven response *in vivo* and autoimmune response in particular where there is a pre-existing and ongoing Th1 driven response. The art teaches that a Th1-Th2 cytokine switch or presence is not correlative of a therapeutic response. In view of the controversy in the art regarding the usefulness of autoantigens as therapeutic agents in the treatment of autoimmune diseases, the lack of teaching of how to use the concept of Th1 to Th2 switch to treat autoimmune disease in general and autoantibodies to treat autoimmune disease by providing "passive immunity" the specification is not enabled for pharmaceutical compositions comprising such for all the reasons made of record.

New Rejections

Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The claim is drawn to an IIS-autoantigen-peptide conjugate. This embodiment is not found in the specification as filed. This issue is best resolved by Applicants pointing to the specification by page and line number where the tripartate conjugate can be found.

Status of Claims

Claims 32-36, 38-39 and 41 stand rejected. Claims 40 and 42-44 are withdrawn from consideration.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia A. Duffy whose telephone number is 571-272-0855. The examiner can generally be reached on M-Th 7:30 am - 6:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Shanon Foley can be reached on 571-272-0898.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Patricia A. Duffy/
Primary Examiner
Art Unit 1645